Annals of Clinical and Analytical Medicine
Original Research

Does the level of serotonin and catecholamine metabolites affect the severity of hyperemesis gravidarum?

Serotonin and catecholamine levels in hyperemesis gravidarum

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Abstract

Aim: Hyperemesis gravidarum (HG) affects most pregnant women and its etiology is unclear. This study investigates the effect of serotonin and catecholamine metabolite levels on hyperemesis gravidarum severity.

Material and Methods: The study was designed as a prospective observational cohort study with 90 pregnant women who applied to the Gynecology and Obstetrics Clinic between September 2019-January 2020. Women between 18 and 42 years of age were divided into three groups; the first group (Group 1) included women diagnosed with severe hyperemesis gravidarum requiring hospitalization, and the second group (Group 2) included women with hyperemesis gravidarum not requiring hospitalization. The third group (Group 3) included healthy pregnant women in the first trimester. The criteria for hospitalization were ketone positivity in urinalysis and intolerance to oral nutrition. The primary outcome of our study was to examine any difference between groups in terms serotonin, adrenaline, dopamine, metanephrine, noradrenaline, and normetanephrine levels.

Results: A total of 90 women were included; severe HG (Group 1) (n=30), mild HG (Group 2) (n=30) and control (Group 3) (n=30). There was no statistically significant difference between the three groups regarding demographic features. Dopamine values were lower in Group 1 and Group 2 than in the control group (19.5 ±10.6 pg/mL; 16.3 ± 11.1 and 30.8 ±12.9, respectively, the Kruskal-Wallis test p<0.001).

Discussion: In this study, dopamine levels were significantly lower than in the control group. Our study may be useful to elucidate the etiology of HG; however, future studies are needed with a large sample size.

Keywords

Hyperemesis Gravidarum, Serotonin, Catecholamine, Dopamine

DOI: 10.4328/ACAM.21613 Received: 2023-01-24 Accepted: 2023-02-25 Published Online: 2023-02-28 Printed: 2023-03-25 Ann Clin Anal Med 2023;14(Suppl 1):S41-44
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This study was approved by the Ethics Committee of Istanbul Research and Training Hospital (Date: 2019-09-11, No: 2019)

Introduction

Hyperemesis gravidarum (HG) is characterized by severe nausea and vomiting in early pregnancy, mostly resulting in maternal nutritional deficiency [1]. Maternal undernutrition has a close relationship with adverse pregnancy outcomes. It is still unclear how HG affects the baby. Throughout history, pregnant women have suffered from HG, and this disease's incidence varies from country to country [1]. Currently, nausea with or without vomiting is expected in early pregnancy, and HG is the most common indication for hospitalization during the first trimester [2]. In addition, HG has an uncertain etiology and is a significant cause of dehydration, acid-base imbalance, ketonuria, and electrolyte imbalances in early pregnancy [3].

The pathogenesis of HG has not yet been elucidated in detail. However, psychological factors, hormonal changes, abnormal gastrointestinal motility, Helicobacter pylori, nutrient deficiencies (e.g., zinc), changes in lipid levels, autonomic changes in the nervous system, genetic factors, and immunological dysregulation are the suggested theories of pathogenesis [4].

The vomiting center in the dorsal part of the Medulla oblongata, named the 'chemoreceptor trigger zone,' is located at the base of the 4th ventricle. It stays outside the blood-brain barrier [5]. This region is sensitive to emetic stimulation of serotonin, dopamine, and its derivative molecules, such as adrenaline and noradrenaline [6, 7] . It is suggested that the serotonin level increases in pregnant women with HG. In addition, 5HT3 receptors are associated with nausea and vomiting, and 5HT3 receptor blockers are used to treat this disorder [8]. On the other hand, there is no study investigating the blood levels of catecholamines and their metabolites in pregnant women with hyperemesis gravidarum. In this study, we aimed to examine whether serotonin and catecholamine levels affect the severity of hyperemesis gravidarum.

Material and Methods

This study was conducted in a prospective observational cohort design in the Gynecology and Obstetrics Clinic between September 2019 and January 2020. The local Ethics Committee approved the study (date: 2019-09-11 number: 2019). All patients gave written informed consent for participation. Women between 18 and 42 years of age were divided into three groups; the first group (Group 1) included women diagnosed with severe hyperemesis gravidarum requiring hospitalization, and the second group (Group 2) included women with hyperemesis gravidarum not requiring hospitalization. The third group (Group 3) included healthy pregnant women in the first trimester. The criteria for hospitalization were ketone positivity in urinalysis and intolerance to oral nutrition. The primary outcome of our study was to examine any differences between groups in terms of serotonin, adrenaline, dopamine, metanephrine, noradrenaline, and normetanephrine levels.

Women were recruited if they did not have any known chronic disease (liver, kidney, heart, hypertension and diabetes etc.), autoimmune disorders; malignancy; multiple pregnancies; the presence of fetal chromosomal and structural anomalies; evidence of active or chronic infection; placental abnormalities. Gestational age was estimated from the first day of the last menstruation period and/or by first-trimester ultrasonography. Venous blood samples of the patients were collected early in the morning from their antecubital veins after 12 hours of fasting and before any treatment, food intake, or intravenous solution administration.

Statistical analysis

SPSS 26.0 program was used for the statistical analysis of the data in this study. In the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov- Smirnov test. ANOVA (Tukey test), Kruskal-Wallis, and Mann-Whitney U tests were used to analyze independent quantitative data. The Chi-square test was used in the analysis of independent qualitative data, and the Fischer test was used when chi-square test conditions were not met. Statistically, the p-value was taken as <0.05 for a significant difference.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 90 pregnant women with a mean week of gestation of 8.9 ± 2.5 were included in the study. Three groups, each consisting of 30 women, were studied: severe HG (Group 1), mild HG (Group 2), and healthy control groups (Group 3). The mean age of the patients was 29.2±5.7 years in the severe HG group, 28.4± 5.6 years in the mild HG group and 27.1±5.6 years in the control group. There were no statistically significant differences between the groups in terms of gravida, parity, gestational week, or body mass index (Table 1).

The mean dopamine level was 19.5±10.6 ng/ml in the severe HG group, 16.3±11.1 ng/ml in the mild HG group, and 30.8±12.9 ng/ml in the control group. Significant differences in dopamine levels were found between severe HG/control groups and mild HG/control groups (p values < 0.05 for all) (Table 2). The mean metanephrine level was 23.1±8.3 ng/ml in severe HG group, 27.5±10.2 ng/ml in mild HG group, and 22.3±8.5 ng/ml in the control group. Significant differences in metanephrine levels were found between mild HG/severe HG groups and mild HG/control groups (p-values < 0.05), there is no statistically significant difference between severe HG and control groups. The mean TSH level was 0.94±0.54 IU/mL in the severe HG group, 1.06±0.52 IU/mL in the mild HG group and 1.73±1.08 IU/mL in the control group. This result also shows that gestational hyperthyroidism is associated with HG.

Table 1. Demographic features of groups.

Features	Group 1 n=30	Group 2 n=30	Group 3 n=30	P value
	Mean ±SD	Mean ±SD	Mean ±SD	
Age, years	29.2±5.7	28.4± 5.6	27.1±5.6	0.317
Gravity	2.5±1.4	2.6±1.6	2.1±1.2	0.374
Parity	1.1±0.9	1.2±1.1	1.0±1.2	0.394
BMI, kg/m^2	25.7±3.4	25.2±2.5	26.0±3.9	0.788
Gestational age, week	9.1±2.4	8.4±2.1	9.2±2.7	0.197
BMI, body mass index				

Table 2. Comparison of the laboratory characteristics of the study groups.

	Group 1 (Severe HG) n=30	Group 2 (Mild HG) n=30	Group 3 (Control) n=30	P value
	Mean ±SD	Mean ±SD	Mean ±SD	
Seratonin ng/ml	315.0± 210.5	268.4±127.7	256.7±95.7	0.721[K]
Adrenalin ng/ml	27.3±15,0	33.7±23.1	35.5±18.8	0.271[K]
Dopamine ng/ml	19.5±10.6[‡]	16.3±11.1[‡]	30.8±12.9	0.000[K]
Metanephrine ng/ml	23.1±8.3*	27.5±10.2	22.3±8.5*	0.048[A]
Noradrenaline ng/ml	216.5±59.0	200.1±72.8	194.8±68.6	0.431[A]
Normetanerphrine ng/ml	82.4±44.6	87.5±34.1	83.5±30.7	0.554[K]
TSH IU/mL	0.94±0.54[‡]	1.06±0.52‡	1.73±1.08	0.003[K]
FT4 ng/dL	0.9±0.3	1.1±0.4	0.9±0.3	0.485[K]
AST U/L	17.6±6.6	16.4±4.2	16.5±3.7	0.837[K]
ALT IU/L	17.7±12.8	14.7±6.6	13.1±5.8	0.486[K]
Sodium mmol/L	135.2±2.1	135.0±1.1	134.9±1.8	0.984[K]
Potassium mmol/L	3.6±0.3	3.5±0.1	3.6±0.3	0.306[K]
Hemoglobin g/dl	11.8±1.5	12.5±0.9	12.0±0.8	0.064[A]
Hematocrit %	34.0±4.4*[‡]	36.6±2.7	36.4±2.7	0.018[K]
Thrombocyte count x10^3 mm^3	253.9±58.8	262.5±48.0	283.9±55.6	0.145[K]

[K] Kruskal-Wallis (Mann-Whitney u test); [A] ANOVA test; AST aspartate aminotransferase, ALT alanine aminotransferase, FT4 free thyroxine, TSH thyroid stimulating hormone; *Difference with Group 2 p<0.05; [‡] Difference with control group p<0.05; Bold values are statistically significant (p<0.05)

Discussion

In the study, we compared the levels of serotonin and catecholamine metabolites in the blood of pregnant women with hyperemesis gravidarum (HG) with the control group. In addition, we analyzed hyperemesis in pregnant women in two groups: severe and mild.

In the study, dopamine values were significantly lower in the hyperemesis gravidarum groups compared to the control group. Metanephrine, an adrenaline metabolite, was slightly higher in the group with nausea and vomiting compared to the control group; but also higher in mild HG than severe HG group (p=0.048). In this study, although mean serotonin levels were higher in the hyperemesis group compared to the control group, it did not reach statistical significance. Few studies investigated the relationship between serotonin levels and hyperemesis gravidarum, but the results are debatable. Borgeat et al. studied serotonin levels by measuring a urinary metabolite of serotonin (hydroxy indole acetic acid) in pregnant women with HG and the control group [9]. No differences in the urinary excretion of serotonin metabolites were noted between the groups. Therefore, the authors concluded that HG was not associated with increased serotonin secretion. In another study, HG group had significantly higher plasma levels of serotonin compared to the control group, and a positive correlation was observed between serotonin levels and the severity of HG [10].

The most prominent finding in our study was the significantly lower dopamine level of pregnant women with HP. There are few data in the literature comparing the dopamine or other catecholamine levels of pregnant women with HG and healthy control groups. Dopamine is a molecule of the catecholamine family, a precursor of catecholamines (adrenaline and noradrenaline), and is associated with multiple physiological functions [11]. Together with its five receptor subtypes, dopamine is closely linked to neurological disorders such as depression, attention deficit–hyperactivity, restless leg syndrome, schizophrenia, Parkinson's disease [12]. Dopamine receptors, especially D2 and D3 receptors, play a role in the pathophysiology of nausea and vomiting. Dopamine receptor antagonists (e.g. metoclopramide) such as serotonin receptor antagonists (eg Ondansetron) reduce nausea and vomiting and are used in the symptomatic treatment of women with HG [13]. In our study, an association was found between low dopamine blood levels and HG. Still, it is not known whether this is a cause or effect relationship and which pathophysiological or biochemical processes are associated with HP. Further studies are needed to explain the mechanism of low dopamine levels in pregnant women with hiperemesis gravidarum.

In addition, among other laboratory data in the study, thyroid-stimulating hormone levels were found to be decreased in pregnant women with hyperemesis. We concluded that this is due to transient hyperthyroidism during pregnancy [14, 15].

When evaluating the findings of our study, it is important to note the limitations of our study, such as the relatively small sample size, and the subjective diagnosis of hyperemesis. We think that the findings of our study should be supported by further studies. In conclusion, the pathophysiology of HG has not been clarified, more molecular and biochemical studies are needed in this regard on this topic.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Ece Sinaci, Sinem Ertas, İsik Kaban. *Does the level of serotonin and catecholamine metabolites affect the severity of hyperemesis gravidarum? Ann Clin Anal Med 2023;14(Suppl 1):S41-44*

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